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Interaction between common breast cancer susceptibility variants, genetic ancestry, and non-genetic risk factors in Hispanic women

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Abstract

Background—Most genetic variants associated with breast cancer risk have been discovered in women of European ancestry, and only a few genome-wide association studies (GWAS) have been conducted in minority groups. This research disparity persists in post-GWAS gene-environment interaction analyses. We tested the interaction between hormonal and lifestyle risk factors for breast cancer, and ten GWAS-identified single nucleotide polymorphisms (SNPs) among 2,107 Hispanic women with breast cancer and 2,587 unaffected controls, to gain insight into a previously reported gene by ancestry interaction in this population.

Methods—We estimated genetic ancestry with a set of 104 ancestry-informative markers selected to discriminate between Indigenous American and European ancestry. We used logistic regression models to evaluate main effects and interactions.

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Results—We found that the rs13387042-2q35(G/A) SNP was associated with breast cancer risk only among postmenopausal women who never used hormone therapy [per A allele odds ratio (OR): 0.94 (95% confidence interval 0.74–1.20), 1.20 (0.94–1.53) and 1.49 (1.28–1.75) for current, former and never hormone therapy users, respectively, P-interaction 0.002] and premenopausal women who breastfed >12 months [OR: 1.01 (0.72–1.42), 1.19 (0.98–1.45) and 1.69 (1.26–2.26) for never, <12 months, and >12 months breastfeeding, respectively, P-interaction 0.014].

Conclusions—The correlation between genetic ancestry, hormone replacement therapy use, and breastfeeding behavior partially explained a previously reported interaction between a breast cancer risk variant and genetic ancestry in Hispanic women.

Impact—These results highlight the importance of understanding the interplay between genetic ancestry, genetics, and non-genetic risk factors and their contribution to breast cancer risk.

Keywords

Breast cancer; Hispanics; Latinas; Gene-environment interaction; Genetic ancestry

Introduction

Breast cancer is a common disease caused by genetic and non-genetic factors (e.g. hormonal and lifestyle factors) and possibly, by the interaction between the two(1). Since the discovery of the high penetrance breast cancer causing genes, *BRCA1* and *BRCA2*, multiple breast cancer genome-wide association studies (GWAS) have unveiled new genetic variants with moderate to small contributions to breast cancer risk[–](2–19). When combined, all common genetic variants explain approximately 30% of familial risk(5), and it has been postulated that an important proportion of the unexplained familial risk might be buried within complex gene by gene and gene by environment interactions(1). Most of the risk-associated variants were originally discovered in samples that included women of European ancestry, and, to our knowledge, only four U.S.-based GWAS have been conducted in or included racial/ethnic minority groups(4, 19–21). The gene by environment interaction analyses that followed the GWAS have also been mostly conducted in populations of European origin(22–34). Studies assessing the relationship between intermediate to low penetrance variants and non-genetic risk factors (from here on referred to as "environmental") have had little success in identifying consistent interactions(22–34). A study including over 70,000 women of European or Asian descent from 24 studies, reported three statistically robust interactions: rs3817198-*LSP1* and parity, rs17468277-*CASP8* and alcohol consumption, and rs11249433-1p11.2 and parity(26). A later study by the same consortium evaluated interactions for an additional set of 47 breast cancer susceptibility loci and reported non-statistically significant interactions for three additional single nucleotide polymorphisms (SNPs) (rs6828523 and height; rs4808801 and number of full-term pregnancies; and rs11242675 and smoking)(34). Beyond the statistical evidence there are no clear biological mechanisms explaining the reported interactions.

We previously found statistically significant interactions between Indigenous American genetic ancestry and genotypes for three out of ten GWAS-discovered breast cancer risk

variants in 2,107 Hispanic/Latina (from here on referred to as Hispanics) women with breast cancer and 2,587 unaffected controls (rs13387042-2q35, rs17157903-*RELN*, and rs7696175-*TLR1*)(35). For these three SNPs, the risk allele showed stronger associations among the group of women with the highest proportion of Indigenous American ancestry. The analyses were aimed at detecting heterogeneity by genetic ancestry based on the underlying hypothesis that if an interaction was observed, it could reflect either a difference in genetic predisposition between populations, or differences in environmental exposures by ancestry that would modify the associations with the genetic variants(35).

In the present study, we investigated multiple environmental breast cancer risk factors to evaluate if the previously observed heterogeneity by ancestry could be due to the correlation between genetic ancestry and those risk factors. First, we tested the interaction between the 3 GWAS-identified breast cancer risk SNPs that had previously shown interaction by ancestry(35) and 15 environmental breast cancer risk factors in a total of 4,694 Hispanic women (2,107 cases and 2,587 controls). Secondly, we assessed the interaction between the 7 other GWAS-identified breast cancer risk SNPs and environmental risk factors to evaluate the possibility of additional interactions.

Materials and Methods

The present analysis was conducted as part of the Breast Cancer Health Disparities Study (36). This collaborative effort to study breast cancer in Hispanic and non-Hispanic White women, combined and harmonized data from two population-based case-control studies conducted in the US: the 4-Corners Breast Cancer Study (4-CBCS) (37) and the San Francisco Bay Area Breast Cancer Study (SFBCS) (38, 39); and a population-based multicenter case-control study conducted in Mexico (MBCS) (40). Details about the Breast Cancer Health Disparities Study have been previously published (35, 36,41–45). All participants signed a written informed consent, and the study was approved by the Institutional Review Board for Human Subjects at each institution. The present analysis is based on 4,697 women of Hispanic/Native American origin living in the U.S. or Mexico with complete genotype and exposure data including 603 Hispanic cases and 730 controls from 4-CBCS, 812 Mexican cases and 989 controls from MBCS, and 692 Hispanic cases and 871 controls from SFBCS.

Genetic Data

The Breast Cancer Health Disparities Study is focused on variants in genes related to inflammation, hormones, metabolism and risk of breast cancer in Hispanic and non-Hispanic White women (36). The genotyping platform included 10 GWAS-identified SNPs associated with breast cancer risk that were published at the time of platform design(3, 6,R11, 12, 14) [rs13387042-2q35 region (G/A), rs17157903-7q22 (C/T) within the *RELN* gene, rs2067980-5q11 (A/G) near the *MRPS30* gene, rs2180341-6q22.1-q22.33 (A/G) within the *RNF146* gene, rs2981582-10q26 (C/T) within the *FGFR2* gene, rs3803662-16q12.1 (C/T) within the *TOX3* gene, rs3817198-11p15.5 (T/C) within the *LSP1* gene, rs7696175-4p14 (C/T) near the *TLR1* gene, rs889312-5q11.2 (A/C) near the *MAP3k1* gene and rs999737-14q23-q24.2 (C/T) within the *RAD51L1* gene]. The platform also included a set of

104 ancestry-informative markers (AIMs) used to infer genetic ancestry among study participants. Details about these AIMs have been previously published(36). All markers were genotyped using a multiplexed bead array assay based on GoldenGate chemistry (Illumina, San Diego, California) attaining a genotyping call rate of 99%. In the present study we analyzed the ten GWAS-identified SNPs associated with breast cancer risk in Europeans or Asians, with a focus on three variants that had previously shown statistically significant interactions with genetic ancestry in Hispanics: rs13387042-2q35, rs17157903-7q22 and rs7696175-4p14(35).

Environmental risk factors (Reproductive/lifestyle)

From available questionnaire data that had been harmonized between the three different studies we selected a set of breast cancer risk factors to explore if the interaction between SNPs and genetic ancestry could be due to the correlation between environmental factors and genetic ancestry. The variables we analyzed were: menopausal status (premenopausal, postmenopausal), age at menopause (<50 or ≥50 years), age at menarche (<11; 11–13; ≥13), age at diagnosis/interview (<40; 40–50; 50–60; >60), alcohol intake (no alcohol; ≤10 gms daily; >10 gms daily), smoking status (ever, never), body mass index (<25; 25–29.9; ≥30 kg/m^2), height (below mean; above mean), waist-to-hip ratio (below mean; above mean), number of full-term pregnancies/age at first-full term pregnancy (no children; 1 or 2 children <25 years old; 1 or 2 children ≥25 years old; ≥3 children <25 years old; ≥3 children ≥25 years old), breastfeeding (no breastfeeding; ≤12 months; >12 months), use of hormone therapy (current, former, never), use of oral contraceptives (ever, never), and family history of breast cancer (yes, no).

Genetic ancestry estimation

Indigenous American ancestry was modeled as continuous or categorical variable depending on the analysis. The cutoffs for three ancestry categories were defined based on sample size as previously described: low Indigenous American ancestry (0–28%), intermediate Indigenous American ancestry (29 to 70%), and high Indigenous American ancestry (71 to 100%)(36). We acknowledge that Hispanic populations would be best modeled as resulting from a three-way admixture process, with a European, an Indigenous American and an African component. However, the African influence in most Hispanic populations is minor (between 0 and 8%) and studies that include women of mostly Mexican or Central American origin, such as ours, do not have sufficient power to evaluate the association of this minor component with health outcomes. We focused the analyses on the Indigenous American/European proportions and estimated genetic ancestry using an unsupervised two-way admixture model. We compared the Indigenous American ancestry estimates obtained with this model, with those obtained with a supervised three-way admixture model in a subset of 1769 Hispanics that were included in a previous study(46) and found that the estimates were highly correlated (Pearson correlation coefficient = 0.94, mean absolute difference between pairs of estimates = 0.09, standard deviation = 0.06).

Statistical Analysis

Indigenous American ancestry proportions were compared between the different categories of environmental risk factors by study and by case/control status using the non-parametric

Kruskal-Wallis equality-of-populations rank test, which is appropriate for variables that deviate from normality, as was the case for genetic ancestry in the analyzed samples. We estimated ancestry-specific odds ratios (OR) for the non-genetic risk factors using logistic regression stratified by ancestry category (low, intermediate, and high Indigenous American ancestry) and adjusting for study, and tested the heterogeneity of the effects by evaluating a logistic regression model that included an environmental risk factor and genetic ancestry interaction term (ExAncestry). We also used logistic regression to evaluate SNP by environmental risk factor interactions (GxE), with adjustment for study, genetic ancestry and age, and to test GxE interactions stratified by ancestry, including age and study as covariates. For those stratified analyses that had results suggestive of an interaction with an environmental risk factor, we conducted likelihood ratio tests (LRT) to compare a model with the SNP by ancestry interaction (GxAncestry) term and adjusted for the environmental factor, to a model with GxAncestry and GxE interaction terms. In the first analyses where we tested the interaction between the three SNPs previously associated with genetic ancestry and environmental risk factors, we considered as statistically significant any interaction with a P value <0.003, which corresponds to a Bonferroni correction for the number of risk factors tested (0.05/15). For analyses that included the other 7 SNPs that did not show interaction by genetic ancestry, we took both the environmental risk factors and the number of SNPs into account when we considered statistical significance. For those analyses we considered as statistically significant a P value $<4.8\times10^{-4}$.

Results

Many risk factors showed associations with breast cancer risk that were statistically significant at the 5% level and concordant with the direction of associations that have been previously reported for these risk factors (Table 1). P values were higher in the low Indigenous American ancestry group, which is to be expected given that the sample size for that group was smaller than that for the other two ancestry groups. We did not find statistically significant heterogeneity by ancestry category for any of the environmental risk factors. However, among postmenopausal women, current use (vs. never use) of hormone therapy showed a positive association in all strata but a suggestive stronger association among Hispanics with high Indigenous American ancestry (P=0.05).

Environmental risk factors and Indigenous American ancestry

Average Indigenous American ancestry differed by risk factor category, and tended to be higher among women with no family history of breast cancer, women with more children at a younger age, a longer duration of breastfeeding, a higher body mass index, a higher waist-to-hip ratio, shorter height, no smoking or alcohol consumption history, no history of oral contraceptive use, with a younger age at diagnosis, menopause before age 50 years, and no history of postmenopausal hormone therapy use (Table 2). Despite the difference in mean Indigenous American ancestry between studies, the direction of association between ancestry and environmental risk factors is similar for most variables.

Interactions of SNPs and environmental factors by Indigenous American ancestry

Assessment of the interaction between the three SNPs that had previously shown an interaction with genetic ancestry and the environmental risk factors showed a statistically significant interaction between the SNP rs13387042-2q35 (G/A) and hormone therapy use among postmenopausal women (P interaction 0.002) and a suggestive interaction with breastfeeding among premenopausal women (P interaction 0.01) (Table 3). We observed that the rs13387042-A variant was associated with increased breast cancer risk among postmenopausal women who had never used hormone therapy and among premenopausal women who breastfed more than 12 months. The strength of the interactions was not affected when other variables were included in the model and LRTs suggested that the models that included the rs13387042-hormone therapy or rs13387042-breastfeeding interaction terms fit the data better than the models that only included the GxAncestry interaction term (hormone therapy use: LRT P = 0.021; breastfeeding: LRT P = 0.028, Table 3). Estrogen receptor (ER) status information was available for 46% of the cases included in the present analysis. There were 720 patients with ER+ tumors and 257 patients with ER- tumors. Given that our analyses were based on stratification by ancestry and risk factors, further stratification by ER status greatly reduced the size of the groups being compared. Even though these exploratory ER status-specific results were inconclusive due to the small sample size, they suggest that the observed associations and interactions in the case/control analyses do not change for ER+ tumors (Supplementary Table S1).

After correcting for multiple testing, no statistically significant interactions were found for the seven SNPs that had not previously shown interactions with genetic ancestry (Supplementary Table S2). For suggestive GxE interactions (P<0.15) involving the three SNPs with previously observed GxAncestry interaction (rs13387042, rs17157903, and rs7696175), we conducted analyses stratified by genetic ancestry to evaluate if the observed GxE interaction affected the previously observed GxAncestry interaction and found no additional statistically significant results (Supplementary Table S3).

Discussion

Our results suggest that the previously reported interaction between a breast cancer risk variant at 2q35 (rs13387042) and genetic ancestry in Hispanics was partially due to the correlation between genetic ancestry and two environmental breast cancer risk factors that affect estrogen levels: use of menopausal hormone therapy and breastfeeding among premenopausal women. We found that the the rs13387042 derived allele (A) only increases breast cancer risk among postmenopausal women who have never been exposed to hormone therapy and among premenopausal women who have breastfed for more than 12 months.

An interaction between breast cancer susceptibility SNP rs13387042-2q35 and menopausal hormone therapy use has been previously reported(26). Nickels et. al. found weak evidence of interaction between the rs13387042 SNP and use of menopausal hormone therapy for combined estrogen/progesterone formulations (P interaction $=2.4\times10^{-3}$)(26). However, they reported a stronger association among current hormone therapy users compared to never users, while we observed an association among never users only. Two other studies that investigated the interaction between previously reported risk SNPs and never/ever use of

hormone therapy(24, 29) did not find statistically significant interactions for the rs13387042 SNP (47, 48). A possible reason for the inter-study incosistencies could be heterogeneity in the definition and categorization of the hormone therapy use variable (e.g. estrogen only, estrogen/progesterone or not specified)(26).

The rs13387042 SNP is located in the short arm of chromosome 2 in an intergenic region. The derived allele A is associated with increased risk of breast cancer and is most common in African populations (77%), has lower frequencies in Europeans (51%) and Mexican Americans (41%), and is less common in Asians (12%) (frequencies from 1000 Genomes Project). The closest known genes are *TNP1* (transition protein 1), *IGFBP5* (insulin-like growth factor binding protein 5), *IGFBP2* (insulin-like growth factor binding protein 2) and *TNS1* (tensin 1/matrix- remodelling-associated protein 6)(12). Recent studies have shown that two polymorphisms that are in strong linkage disequilibrium (LD) with rs13387042 (rs6721996 and rs4442975, r2=0.92) are associated with expression of the *IGFBP5* gene, with decreasing expression of *IGFBP5* with increasing number of A alleles(49, 50). One of these studies was a fine-mapping effort that included functional analyses, and concluded that the rs4442975 SNP was the most likely functional variant(50). It has been reported that *IGFBP5* is expressed in breast cancer and breast cancer cell lines, and it is produced by estrogen receptor (ER)-alpha positive tumors, which is concordant with the previous observation that the rs13387042 polymorphism is more strongly associated with risk of ER positive disease(12). *IGFBP5* has been shown to inhibit cell proliferation via an insulin growth factor (*IGF*)-dependent mechanism(51). Adding to this, estrogen-induced transcriptional activity of ER-alpha is reduced by *IGFBP5* expression independent of *IGF*(51). The observation that the rs13387042 SNP is associated with breast cancer risk only among women who have never used hormone therapy is counterintuitive and needs to be further explored. A possible explanation could be that in a low estrogenic environment (such as that of postmenopausal women who do not use hormone therapy or women who breastfeed for more than a year), the level of expression of *IGFBP5* becomes crucial in limiting cell growth and proliferation, while in an estrogen-rich environment, the inhibitory effect of *IGFBP5* might be overridden by other estrogen dependent regulatory mechanisms. We did not find strong evidence of heterogeneity of GxE interaction by tumor ER status, but the analysis was limited by the small size of the compared categories after ER status stratification.

We were not able to explain the previously reported gene by ancestry interactions for two SNPs (rs17157903 and rs7696175) and none of the remaining polymorphisms analyzed show statistically significant GxE interactions. We cannot dismiss the possibility that our study might have failed to detect interactions between these SNPs and non-genetic risk factors due to reduced power after accounting for multiple testing. In addition, we want to acknolwedge that the present analysis only included a small subset of all SNPs that have been reported to be associated with breast cancer risk to date (2–19), which was determined by the limited number of published associated polymorphisms at the time of platform design. Despite these limitations, our study is the largest study to date that tested the interaction between breast cancer GWAS-identified polymorphisms and non-genetic risk factors in Hispanic women.

In summary, in this study we present the results of a breast cancer GxE interaction analysis in Hispanic women. We found that the association between the rs13387042-2q35 polymorphism and breast cancer risk is modified by hormone therapy use among postmenopausal women and by breastfeeding among premenopausal women. The present analysis illustrates how genetic ancestry in admixed populations might not only reflect population differences in genetic predisposition, but also differences in environmental exposures that together with genetic factors can influence breast cancer risk. Future research should confirm the reported interactions as well as the negative results and properly account for the complex interactions between environment, genetics, and behavior in populations of mixed descent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Association between breast cancer risk and non-genetic risk factors by Indigenous American ancestry in Hispanics from the Breast Cancer Health Disparities Study

		Low Indigenous American ancestry (N=557)			Interm. Indigenous American ancestry (N=3098)			High Indigenous American ancestry (N=1078)		
Category		**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age at dx/interview (Ref: ≤40)	41–50	1.39	0.78–2.48	0.258	**1.47**	**1.15–1.85**	**0.001**	1.13	0.77–1.63	0.524
	51–60	1.11	0.62–1.98	0.715	**1.38**	**1.08–1.75**	**0.009**	1.03	0.69–1.51	0.886
	>60	1.36	0.75–2.43	0.301	**1.36**	**1.06–1.74**	**0.014**	1.10	0.72–1.66	0.661
Family history BC (Ref: No)	Yes	**1.71**	**1.07–2.73**	**0.023**	**1.37**	**1.08–1.72**	**0.008**	**2.63**	**1.38–4.98**	**0.003**
Anthropometrics										
BMI (kg/m^2) (Ref: <25)	25–29	0.83	0.54–1.28	0.406	**0.74**	**0.60–0.90**	**0.004**	0.74	0.51–1.06	0.104
	≥30	0.81	0.53–1.22	0.318	**0.62**	**0.51–0.75**	**<0.001**	**0.69**	**0.47–0.98**	**0.041**
W-H ratio (Ref: Below the mean)	Above the mean	1.09	0.73–1.61	0.672	1.07	0.91–1.24	0.378	0.79	0.59–1.06	0.122
Height (Ref: Below the mean)	Above the mean	1.03	0.70–1.51	0.873	**1.19**	**1.02–1.37**	**0.02**	**1.43**	**1.07–1.88**	**0.013**
Lifestyle										
Smoking (Ref: Never)	Ever	1.13	0.76–1.66	0.539	1.08	0.91–1.27	0.35	1.04	0.76–1.42	0.789
Daily alcohol intake (Ref: None)	≤10gms/day	0.95	0.64–1.40	0.801	1.01	0.83–1.23	0.903	0.88	0.43–1.80	0.735
	>10gms/day	1.49	0.88–2.51	0.137	**1.41**	**1.02–1.94**	**0.034**	0.37	0.03–3.54	0.392
Reproductive characteristics										
Parity/AFFTP (Ref: nulliparous)	1–2 children/<25 years of age	1.09	0.58–2.03	0.794	**0.69**	**0.50–0.93**	**0.018**	**0.56**	**0.33–0.95**	**0.033**
	1–2 children/≥25 years of age	1.34	0.74–2.43	0.331	**0.69**	**0.51–0.94**	**0.018**	0.91	0.53–1.53	0.728
	≥3 children/<25 years of age	0.97	0.54–1.69	0.903	**0.43**	**0.32–0.56**	**<0.001**	**0.57**	**0.36–0.89**	**0.016**
	≥3 children/≥25 years of age	1.32	0.63–2.70	0.457	**0.54**	**0.38–0.75**	**<0.001**	0.60	0.32–1.08	0.091
Breastfeeding if parous (Ref: No)	≤12 months	0.85	0.54–1.30	0.453	0.86	0.71–1.03	0.108	0.75	0.51–1.11	0.156
	>12 months	0.70	0.43–1.12	0.137	**0.56**	**0.45–0.68**	**<0.001**	**0.52**	**0.33–0.80**	**0.003**

		Low Indigenous American ancestry (N=557)			Interm. Indigenous American ancestry (N=3098)			High Indigenous American ancestry (N=1078)		
Category		**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
Oral contraceptive use (Ref: Never)	Ever	1.13	0.78–1.62	0.512	1.05	0.90–1.20	0.544	1.12	0.87–1.43	0.376
Age at menarche (Ref: ≤11 yrs.)	12 to 13	1.20	0.80–1.80	0.370	0.85	0.70–1.01	0.078	1.04	0.75–1.44	0.798
	>13	0.83	0.51–1.32	0.434	**0.80**	**0.66–0.97**	**0.03**	0.80	0.55–1.13	0.209
Menopause (Ref: Premenopausal)	Postmenopausal	0.97	0.67–1.38	0.853	1.01	0.87–1.17	0.857	0.91	0.70–1.16	0.438
Postmenopausal women only			**N=325**			**N=1793**			**N=591**	
Age at menopause (Ref: age ≤50)	. ≥50 yrs.	1.22	0.75–1.96	0.409	1.12	0.91–1.37	0.276	1.17	0.81–1.69	0.392
BMI (Ref: <25)	25–29	0.93	0.52–1.65	0.816	0.83	0.63–1.09	0.193	0.86	0.50–1.46	0.585
	≥30	0.67	0.38–1.16	0.154	**0.67**	**0.51–0.86**	**0.003**	0.83	0.49–1.39	0.476
Hormone therapy use (Ref: Never)*	Former	**0.64**	**0.36–1.15**	**0.137**	**0.88**	**0.69–1.13**	**0.321**	**1.19**	**0.76–1.86**	**0.456**
	Current	**2.03**	**1.18–3.47**	**0.01**	**1.71**	**1.33–2.19**	**<0.001**	**5.90**	**2.13–16.33**	**0.001**

Abbreviations: Interm: Intermediate; dx: diagnosis; BC: breast cancer; BMI: body mass index; W-H ratio: Waist to hip ratio; AFFP: Age at first full-term pregnancy.

*P value for interaction between ancestry category and reproductive/lifestyle variable = 0.05

Table 2

Mean (standard deviation) Indigenous American ancestry among controls in each study by levels of risk factors in Hispanics from the Breast Cancer Health Disparities Study (differences in ancestry significant at the 5% level or lower are in **bold**)

		4-CBCS		MBCS		SFBCS	
Variable		**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Age at dx/interview	≤40	**79**	**0.45 (0.17)**	**108**	**0.70 (0.19)**	63	0.40 (0.21)
	41–50	**202**	**0.42 (0.18)**	**299**	**0.69 (0.19)**	238	0.45 (0.20)
	51–60	**177**	**0.43 (0.17)**	**237**	**0.65 (0.20)**	190	0.41 (0.19)
	>60	**151**	**0.40 (0.16)**	**172**	**0.64 (0.20)**	207	0.41 (0.18)
Family history BC	No	452	0.42 (0.17)	**766**	**0.68 (0.19)**	600	0.43 (0.19)
	Yes	104	0.41 (0.17)	**50**	**0.61 (0.18)**	98	0.39 (0.20)
Anthropometrics							
BMI (kg/m^2)	<25	**193**	**0.38 (0.17)**	160	0.64 (0.21)	**139**	**0.37 (0.19)**
	25–29	**210**	**0.43 (0.16)**	330	0.68 (0.18)	**228**	**0.44 (0.19)**
	≥30	**191**	**0.45 (0.17)**	311	0.67 (0.19)	**330**	**0.43 (0.19)**
Waist-to-hip ratio	Below mean	**380**	**0.40 (0.17)**	**229**	**0.63 (0.19)**	**446**	**0.41 (0.19)**
	Above mean	**205**	**0.46 (0.16)**	**564**	**0.68 (0.19)**	**233**	**0.45 (0.19)**
Height	Below mean	**230**	**0.45 (0.17)**	**506**	**0.70 (0.19)**	**267**	**0.48 (0.18)**
	Above mean	**367**	**0.40 (0.17)**	**295**	**0.61 (0.19)**	**412**	**0.39 (0.19)**
Lifestyle							
Smoking	Never	**395**	**0.44 (0.17)**	**604**	**0.69 (0.19)**	**298**	**0.44 (0.19)**
	Ever	**201**	**0.37 (0.16)**	**212**	**0.62 (0.20)**	**148**	**0.40 (0.18)**
Daily alcohol intake	Never	385	0.43 (0.17)	NA	NA	**435**	**0.45 (0.19)**
	≤10gms/day	173	0.39 (0.16)	NA	NA	**171**	**0.41 (0.20)**
	>10gms/day	39	0.40 (0.18)	NA	NA	**92**	**0.34 (0.16)**
Reproductive characteristics							

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		4-CBCS		MBCS		SFBCS	
Variable		**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Parity/AFFTP	Nulliparous	57	0.41 (0.17)	**91**	**0.65 (0.19)**	**81**	**0.42 (0.20)**
	1–2 children/<25 years of age	126	0.42 (0.14)	**106**	**0.68 (0.20)**	**127**	**0.41 (0.19)**
	1–2 children/≥25 years of age	113	0.39 (0.17)	**165**	**0.66 (0.20)**	**138**	**0.38 (0.21)**
	≥3 children/<25 years of age	250	0.43 (0.18)	**356**	**0.69 (0.19)**	**275**	**0.46 (0.17)**
	≥3 children/≥25 years of age	51	0.43 (0.16)	**80**	**0.61 (0.20)**	**76**	**0.41 (0.20)**
Breastfeeding	Never	214	0.41 (0.15)	**102**	**0.67 (0.18)**	223	0.42 (0.19)
	≤12 months	173	0.41 (0.17)	**517**	**0.66 (0.20)**	231	0.41 (0.20)
	>12 months	153	0.45 (0.20)	106	0.73 (0.18)	163	0.44 (0.18)
Oral contraceptive use	No	**270**	**0.45 (0.17)**	404	0.68 (0.19)	**236**	**0.45 (0.18)**
	Yes	**320**	**0.39 (0.16)**	409	0.66 (0.19)	**456**	**0.41 (0.19)**
Age at Menarche (yrs.)	≤11	135	0.40 (0.15)	171	0.66 (0.19)	195	0.42 (0.19)
	11 to 13	283	0.42 (0.18)	395	0.67 (0.20)	324	0.42 (0.20)
	>13	178	0.43 (0.17)	238	0.68 (0.19)	176	0.43 (0.18)
Menopause	Premenopausal	235	0.43 (0.18)	**345**	**0.69 (0.18)**	256	0.44 (0.19)
	Postmenopausal	360	0.41 (0.16)	**471**	**0.66 (0.20)**	379	0.42 (0.18)
Postmenopausal							
Menopause at age ≥50 yrs.	No	233	0.41 (0.16)	319	0.67 (0.19)	179	0.42 (0.17)
	Yes	109	0.40 (0.16)	155	0.65 (0.21)	140	0.40 (0.19)
Hormone therapy use	Current	142	0.39 (0.16)	20	0.58 (0.20)	155	0.40 (0.18)
	Former	65	0.41 (0.15)	90	0.63 (0.18)	76	0.41 (0.18)
	Never	150	0.43 (0.16)	356	0.67 (0.20)	141	0.43 (0.18)

Abbreviations: 4-CBCS: 4-Corners Breast Cancer Study; MBCS: Mexico Breast Cancer Study; SFBCS: San Francisco Bay Area Breast Cancer Study; dx: diagnosis; BC: breast cancer; BMI: body mass index; AFFTP: Age at first full-term pregnancy.

Table 3

Association between rs13387042 (2q35) and breast cancer risk, stratified by Indigenous American genetic ancestry, hormone therapy use, and breastfeeding in Hispanic women from the Breast Cancer Health Disparities Study

		N	Odds Ratio*	95% CI	P value	P Interaction	P LRT**
Stratified by Indigenous American ancestry							
Low		557	1.10	0.87–1.39	0.441	0.051	
Intermediate		3098	1.17	1.06–1.30	0.003		
High		1078	1.47	1.17–1.83	0.001		
Stratified by hormone therapy use in postmenopausal women							
Current		575	0.94	0.74–1.20	0.644	0.002	
Former		592	1.20	0.94–1.53	0.134		
Never		1521	1.49	1.28–1.75	<0.001		
Stratified by breastfeeding in premenopausal women							
Never		324	1.01	0.72–1.42	0.96	0.014	
≤12 months		923	1.19	0.98–1.45	0.076		
>12 months		424	1.69	1.26–2.26	<0.001		
Stratified by hormone therapy use and genetic ancestry in postmenopausal women							
Current	Low	113	1.10	0.64–1.87	0.733	0.373	0.021
	Intermediate	439	0.90	0.67–1.20	0.473		
	High	22	0.05	0.00–2.41	0.128		
Former	Low	80	0.57	0.27–1.21	0.144	0.016	
	Intermediate	407	1.24	0.92–1.67	0.156		
	High	101	1.39	0.63–3.02	0.413		
Never	Low	127	1.64	0.97–2.73	0.06	0.988	
	Intermediate	929	1.29	1.05–1.57	0.015		
	High	465	1.72	1.21–2.42	0.002		

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		N	Odds Ratio*	95% CI	P value	P Interaction	P LRT**
Stratified by breastfeeding and genetic ancestry in premenopausal women							
Never	Low	25	0.85	0.24–2.96	0.799	0.803	0.028
	Intermediate	241	1.03	0.69–1.52	0.89		
	High	56	1.44	0.43–4.84	0.56		
≤12 months	Low	88	0.87	0.44–1.73	0.692	0.113	
	Intermediate	542	1.1	0.86–1.41	0.463		
	High	293	1.38	0.91–2.11	0.130		
>12 months	Low	47	1.52	0.60–3.82	0.377	0.917	
	Intermediate	292	1.69	1.20–2.38	0.003		
	High	83	2.22	0.81–6.10	0.122		

*OR per additional A allele

**P likelihood ratio test comparing the model with interaction between SNP and ancestry, adjusted for the environmental risk factor, to a model with SNP by ancestry and SNP by envionmental risk factor interaction.